

Epidemic of Mucormycosis in COVID-19 Pandemic: A Position Paper

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Abstract

During the second wave of COVID-19 pandemic, there is a sudden increase in number of cases mucormycosis infection in India. This communication by the Tropical Neurology subsection expert group of the Indian Academy of Neurology (IAN) describes the clinical and diagnostic features, treatment of the disease and gives recommendations about the ways forward.

Keywords: Mucormycosis, rhino-orbito-cerebral syndrome, COVID-19

INTRODUCTION

Mucormycosis belongs to a group of saprophytic fungi growing on decaying vegetation and food containing high sugar content. Diabetes and acidosis are the most important predisposing factors. The other predisposing factors include malignancy, immunosuppression, post-organ transplantation, hemosiderosis, and the use of high doses of steroids. The regional differences in the occurrence of mucormycosis may vary depending on the nature of the population, comorbidities, and medical infrastructure to diagnose and treat these infections. In India, most of the information is from tertiary care teaching hospitals.^[1,2] However, cases have been seen in all parts of the country.

In the second wave coronavirus disease 2019 (COVID-19) pandemic, high frequency of mucor infections has been seen. This could be due to COVID-19 associated illness requiring high and prolonged steroids use leading to diabetes mellitus (DM), immunosuppression, elevated ferritin leading to high iron load, acidosis, endothelial damage and use of multiple broad-spectrum antibiotics to prevent or treat secondary infections.^[3,4] Since India has the second-highest number of COVID-19 cases,^[5] the second-highest number of diabetes mellitus patients^[6] and the highest incidence of mucormycosis,^[7] it is expected that mucor will be seen in India in large numbers especially in COVID-19 patients.

Indeed, in last 3-4 months, a large number of cases of mucormycosis are seen by various specialists in India. John TN et al reported, 71% of patients with mucormycosis with COVID-19 were from India.^[3] It is appropriate that the data on mucor in India should be generated and rational guidelines developed for the management of mucormycosis in COVID-19 patients. This communication is an effort by

the Tropical Neurology subsection expert group of the Indian Academy of Neurology (IAN).

CLINICAL PRESENTATION

Mucor infection causes pulmonary, cutaneous, and rhino-orbito-cerebral involvement. The characteristic neurological clinical syndrome of mucormycosis is the rhino-orbito-cerebral syndrome, which is also caused by other angio-invasive fungi including aspergillosis and *Pseudallescheria boydi*. The presenting symptoms of the rhino-orbito-cerebral syndrome include headache, facial pain, eye pain, facial numbness, diplopia with varying degrees of ophthalmoplegia, ptosis, proptosis vision loss with and without papilledema, nasal discharge, epistaxis, and loosening of teeth [Box 1]. Black discolouration of skin and mucosa along with ulceration and discharge from the nose, palatal mucosa are typical of mucor infection. In the nervous system, mucor causes necrotizing tissue damage and thrombosis of neighboring vessels; cavernous sinus and internal carotid artery.

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DIAGNOSIS

Computed tomography (CT) or magnetic resonance imaging (MRI) should include imaging of paranasal sinuses, orbits, brain, and intracranial vessels. CT scan demonstrates bone dehiscence or destruction and can be considered the first modality for imaging. MRI is useful in demonstrating the optic nerve, intracranial and vascular invasion. The following features suggest fungal infection:

- Non-enhancing hypointense mucosa over nasal turbinate and nasal septum (black turbinate sign)^[8]
- Concomitant sinus and orbit involvement
- Bone erosion or destruction
- Associated cavernous sinus involvement, internal carotid artery involvement in cavernous sinus, ischemic strokes.

Since there is no biomarker for mucor, the diagnosis is achieved by demonstrating fungus, either in the tissue obtained from nasal scrapping or from the tissue obtained during surgery. Various modalities include

- Fungal stains Potassium hydroxide (KOH) and Calcofluor
- Fungal culture
- Histopathology
- Polymerase chain reaction (PCR) based molecular diagnosis from biopsied tissue sample and/or culture.^[9]

MANAGEMENT

Since mucormycosis carries 50% mortality,^[1,3] treatment should be prompt and includes antifungal drugs, surgical debridement, and correction of underlying metabolic abnormalities including hyperglycemia, ketosis, acidosis, and other metabolic abnormalities [Figure 1].

MEDICAL MANAGEMENT

The anti-fungal drug of choice is amphotericin B. The liposomal form of amphotericin B 5-10 mg/kg/day is recommended in view of better tolerability.^[10] In case of the liposomal form, slow titration of amphotericin is not recommended and the target dose is started right from the day one. More than 10 mg/kg of amphotericin does not increase the serum level; therefore, a higher dose is not recommended. If the cost of liposomal amphotericin is a limiting factor, conventional amphotericin B or amphotericin deoxycholate can be used. The efficacy of conventional amphotericin B/amphotericin deoxycholate is not inferior to the liposomal form,^[11] but has higher side effects. The serum half-life of conventional

amphotericin is 12-24 hours with peak serum concentration lasting for 6-8 hours. It is used in a dose of 0.3-1.5 mg/kg/day infusion over 1 to 4 hours. It is recommended to begin intravenous therapy with a 1-mg test dose. Amphotericin B can be infused over one to two hours in patients with adequate renal function.^[12] The side effects of amphotericin include nephrotoxicity (up to 80%), hypokalemia, hypomagnesemia, normocytic normochromic anemia and flu-like allergic reaction. Central nervous system (CNS) toxicity limits its intra-thecal use. Occasionally life-threatening reactions such as anaphylaxis, acute hepatic failure, seizure, ventricular fibrillation and cardiac arrest may occur. Nephrotoxicity of amphotericin is related to its peak serum concentrations especially if the cumulative dose exceeds 5-10 gm. To minimize the nephrotoxicity, hydration with one liter normal saline infusion before the amphotericin may be helpful.^[13] Patients should be monitored by frequent urinalyses (red and white blood cell casts), serum creatinine, creatinine clearance, serum potassium, and electrocardiogram (ECG). Idiosyncratic reactions and severe toxicity may necessitate discontinuation of amphotericin. Amphotericin should be avoided in patients who are hypersensitive to it unless this is the only possible therapy in the face of a life-threatening fungal infection. In rhino-orbital mucor, orbital amphotericin injections and irrigation of paranasal sinuses with amphotericin have been tried.

Other drugs used in the treatment of mucormycosis are posaconazole (300 mg twice daily for three days followed by 300 mg daily, orally) and isavuconazole (200 mg twice daily on the first day followed by 200 mg daily).^[10] In an open-label study isavuconazole was showed efficacy similar to amphotericin.^[14] Oral formulation can be used for a long duration; up to 180 days.^[6] Other antifungal drugs (fluconazole, voriconazole, caspofungin) are not useful in the treatment of mucormycosis.

SURGICAL MANAGEMENT

Surgical treatment includes debridement, or surgical excision of necrotic tissue, abscess osteomyelitis, etc., Depending on the site of involvement, oto-laryngo-rhinologist (ENT) surgeon, ophthalmologist, dental/ oral surgeon, and/or neurosurgeon should be part of surgical team. Functional endoscopic sinus surgery (FESS) and orbital debulking are commonly required surgeries in mucormycosis. Surgery at an early stage is better than late because drugs do not reach the necrotic tissue. Good surgical support is crucial for a good outcome of mucor patients. Check endoscopy or surgical exploration needs to be repeated on a case-to-case basis depending on the response to the treatment.

The duration of therapy is not known and decided on a case-to-case basis. The treatment with amphotericin is recommended for 4-6 weeks. This can be followed by posaconazole or isavuconazole for few more weeks as maintenance therapy.^[15] Treatment can be stopped if there is clinical and radiological

Box 1: Pointers to mucor infection in a COVID-19 or post-COVID-19 patient (within 2 months)

New-onset headache
Facial pain, facial numbness
Eye pain, diplopia, vision loss
Orbital swelling, lid edema
Nasal congestion, black nasal discharge, and epistaxis
Loosening of teeth

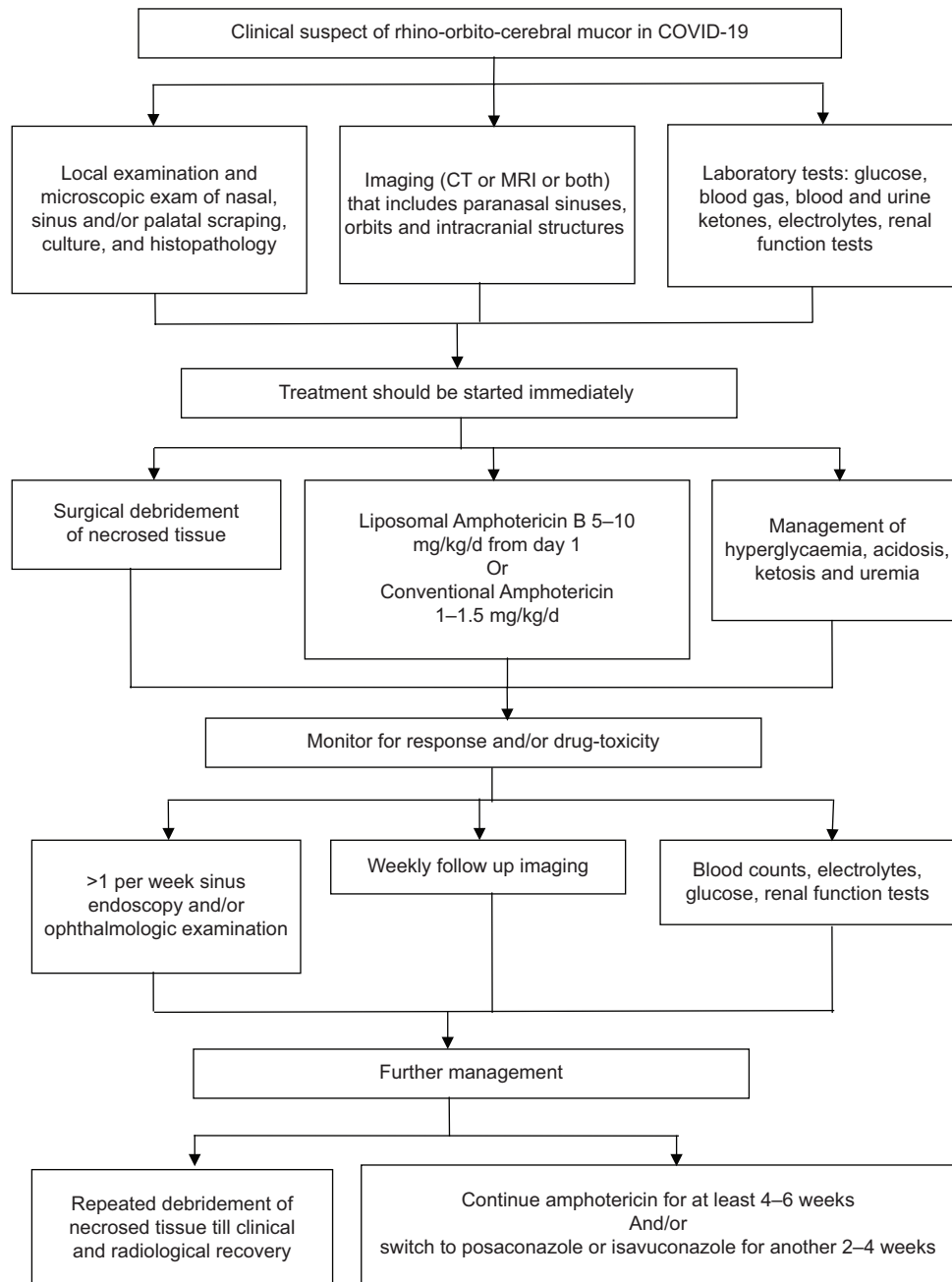


Figure 1: Flow chart of management of mucormycosis in COVID-19

clearance, permanent reversal of immunosuppression and substantial improvement.^[10]

OUTCOME

As the disease is known to be aggressive, mortality is more than 50%.^[1] The mortality increases to 80% with an intracranial extension of the disease.^[11] Other risk factors for poor prognosis are shorter duration of symptoms and shorter duration of therapy, while combined medical and surgical treatment has better survival.^[1] Larger studies are needed in mucormycosis in COVID-19 to know outcome and prognostic markers.

WAY FORWARD

Since there is a sudden surge of cases of mucor in COVID-19, there is a need to improve awareness among treating physicians about early diagnosis and treatment. There is marked variability in the frequency of mucormycosis cases reported in different regions in India including the COVID-19 patients. A national registry and larger studies may help in providing useful data. Abnormalities in the immune system in COVID-19, sensitivity patterns of fungus, and the reasons for the sudden surge in cases in the second wave of the pandemic need to be studied. To prevent the occurrence of mucormycosis, rational use of steroids and antibiotics for the shortest possible time,

meticulous glycemic control, and adequate attention toward ventilators and tubing are necessary. The involvement of microbiologists in monitoring the ward, ICU, and hospital environment to account for fungal diseases is also crucial.

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Conflicts of interest

There are no conflicts of interest.

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